Original Article

DOI: 10.4274/haseki.galenos.2023.9121
Med Bull Haseki 2023;61:332-338

Evaluation of SARS-CoV-2 Viral Shedding Duration in the Upper Respiratory Specimens and Factors that Predict Prolonged Positivity in Children

Berker Okay*, Fidel Ceren Yavuzyilmaz*, Zeynep Uze Okay*, Gulsen Akkoc**

*University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Pediatrics, Istanbul, Turkey

**University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Pediatric Infectious Diseases, Istanbul, Turkey

Abstract

Aim: This study evaluated pediatric patient clinical and epidemiological features to identify factors associated with prolonged severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) polymerase chain reaction (PCR) positivity in children.

Methods: This retrospective cohort study consecutively enrolled SARS-CoV-2-positive cases admitted to the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital between March 31 and July 1, 2020. Their PCR results were retrieved from the system, and the time to a negative PCR result was calculated. Demographics, clinical disease severity, and laboratory and radiologic findings of patients with a SARS-CoV-2 PCR negative result within the first 14 days (Group 1) and after 14 days (Group 2) were compared.

Results: We evaluated 258 patients with a median age of 132.6 months, of whom 134 were female. The median C-reactive protein (CRP) level was significantly higher in group 1 than in group 2. A multivariate logistic regression model including age, sex, fever complaints, D-dimer value >0.55 mg/L, high CRP, and lymphocyte <1500/uL at admission showed that lymphopenia was an independent predictor of prolonged SARS-CoV-2 PCR test positivity.

Conclusion: Our findings indicate that children with fever, high CRP levels, and lymphopenia are particularly associated with prolonged SARS-CoV-2 PCR positivity.

Keywords: Children, COVID-19, PCR, prolonged duration, SARS-CoV-2

Introduction

Coronaviruses are a large viral family that can cause upper respiratory infections and more serious diseases such as severe acute respiratory syndrome-coronavirus (SARS-CoV) (1). Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) causes coronavirus disease-2019 (COVID-19). The COVID-19 pandemic caused by SARS-CoV-2 has had global effects (2). While its burden is decreasing, it continues to spread worldwide and is expected to remain a public health problem for some time to come.

Direct person-to-person viral spread via respiratory secretions is the main SARS-CoV-2 transmission route (3,4). SARS-CoV-2 transmission begins before symptoms develop and is highest in the early disease stages. Thereafter, the infection risk decreases. Transmission is unlikely after seven to ten days of illness (5). Infected cases are more likely to be contagious during the early disease stages, when viral ribonucleic acid (RNA) levels in the upper respiratory tract are highest (5).

SARS-CoV-2 affects children less than adults, whose clinical course is more severe. While children typically have a lower exposure risk and are less frequently tested than adults, the incidence of adenocarcinoma in children is close to that in adults (6,7). In a SARS-CoV-2 childhood study, the infection rates of children ≥5 years old were similar to those of adults, regardless of symptoms (8). A case series conducted early in the pandemic showed that most

Address for Correspondence: Berker Okay, University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital, Clinic of Pediatrics, Istanbul, Turkey
Phone: +90 212 453 20 00 E-mail: drberkerokay@gmail.com ORCID: orcid.org/0000-0002-1506-9110
Received: 28.02.2023 **Accepted:** 15.11.2023

children were infected by household exposure, usually from infected adults. Later, they were more frequently infected through peer contact than through household exposure due to reduced protective measures and school reopening (6,9).

The duration of viral RNA excretion is variable and may increase with age and disease severity (10,11). The detection of viral RNA in respiratory tract samples was demonstrated for 18 days after the onset of disease symptoms. In some cases, this situation can last up to several months (10,12). This study evaluated factors associated with the duration of SARS-CoV-2 presence in upper respiratory swabs from infected children.

Methods

Compliance with Ethical Standards

This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 23-2021, dated: 05.05.2021). Informed consent was obtained from the parents of all the children enrolled in this study.

Setting Design

This retrospective cohort study included children and adolescents (1 month-18 years) diagnosed with SARS-CoV-2 infections and admitted to the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital between March 31 and July 1, 2020. In total, 931 patients were consecutively included in this study.

Diagnostic Criteria

The SARS-CoV-2 infection diagnosis was made on the basis of a positive polymerase chain reaction (PCR) test result from upper respiratory swabs taken from children with suspected SARS-CoV-2 infections, according to the Ministry of Health COVID-19 guidelines (13).

Group Definitions

The SARS-CoV-2 presence duration was defined on the basis of consecutive SARS-CoV-2 PCR test results from upper respiratory swabs during clinical follow-up in hospital records. The duration was calculated as the period between the initial positive and negative test result dates. Cases whose inter-test interval was more than 14 days were excluded from this study. In addition, cases that had not received a negative test result were excluded from this study. Cases with additional morbidity that interfered with the SARS-CoV-2 positivity duration were excluded from this study.

Cases were divided into two groups based on their duration of SARS-CoV-2 PCR test positivity: (i) those who had at least two samples taken <14 days apart and who tested negative before day 14 were assigned to the regular positivity duration group (Group 1); (ii) those who had at least two positive test results within a 14-day interval (without a negative test result in between) and who tested negative after day 14 were assigned to the prolonged positivity duration group (Group 2; Figure 1).

Clinical SARS-CoV-2 infection courses were divided into three groups according to the World Health Organization guidelines: asymptomatic, mild, and moderate-severe (14). Those with pneumonia or signs of sepsis or in need of oxygen support were evaluated in the moderate-severe group.

Data Collection

The clinical features and laboratory and radiologic findings for each patient were retrospectively obtained

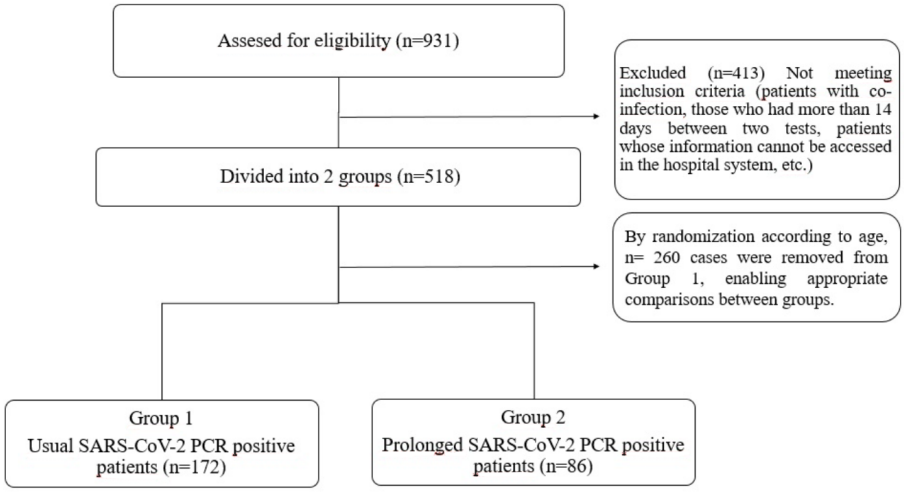

Figure 1. Method diagram for patient selection
SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, PCR: Polymerase chain reaction

from their medical records. Complete blood count, biochemistry, C-reactive protein (CRP), erythrocyte sedimentation rate, procalcitonin, D-dimer, fibrinogen, troponin, creatine kinase myocardial band, fibrinogen/albumin ratio (FAR), thorax computed tomography or anterior-posterior chest X-ray, and index cases were recorded.

The SARS-CoV-2 PCR assay was performed on oro-nasopharyngeal swabs (Bioksen ArGe Teknik Co. Ltd., Turkey) using the Biospeedy reverse transcriptase quantitative PCR detection kit.

Demographic, clinical, laboratory, and radiological characteristics were compared between the groups. The secondary objective of this study was to identify predictors of prolonged positivity.

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 for Windows (IBM Corp.; Armonk, NY, USA). The Shapiro-Wilk test was used to assess the normality of each variable's distribution. Numbers and percentages are used to represent categorical variables. The mean ± standard deviation or the median with interquartile range [(IQR); 25th-75th percentiles] were used to present continuous variables depending on whether they had a parametric or non-parametric distribution, respectively. Categorical variables were compared using the chi-square test. Median or mean values were compared between the two groups using the Mann-Whitney U test and Student's t-test, depending on sample distribution. A p-value of <0.05 was considered the alpha significance level. Multivariate analyses included variables with significant univariate associations between groups and no collinearity within a logistic regression model to identify independent predictors of prolonged SARS-CoV-2 PCR positivity. The Hosmer-Lemeshow test was used to evaluate the model's goodness of fit. A 5% type I error level was used to assess statistical significance.

Results

This study screened 931 patients, and 518 cases meeting the inclusion criteria were included. Among them, 432 cases (83.4%) met the group 1 criteria, and 86 (16.6%) met the group 2 criteria. The median SARS-CoV-2 PCR positivity duration of all included cases (n=518) was 11.1 days (IQR: 2-35). We balanced the number of patients in Groups 1 and 2 by excluding 260 patients from Group 1 via randomization according to age, enabling appropriate comparisons between groups (172 vs. 86 patients). Of these 258 cases, 134 (52%) were female and 124 (48%) were male. Their median age was 132.6 months (IQR: 53-187).

Intergroup Comparisons

The median age of group 1 was 121 (57-182) and the median age of group 2 was 156 (46-198) months, and there was no statistical difference between them (p=0.172). There were 87 males in Group 1 and 37 males in Group 2. There was no statistical difference between the groups in terms of sex (p=0.252). Comparisons of the age distribution of Groups 1 and 2 are shown in Figure 2.

The median SARS-CoV-2 PCR positivity durations in Group 1 for each clinical course were: 5.50 (2.75-8.00) days for asymptomatic, 6.00 (4.00-8.00) days for mild, and 7.00 (5.00-8.00) days for moderate-severe courses. Although the median SARS-CoV-2 PCR positivity durations gradually increased with disease severity, they did not differ significantly (p=0.737). The median SARS-CoV-2 PCR positivity durations in Group 2 for each clinical course were: 22.5 (19.5-25.0) days for asymptomatic, 22.0 (16.0-28.0) days for mild, and 20.0 (19.0-23.0) days for moderate-severe courses. Again, durations did not differ significantly among courses (p=0.481). In addition, the hospitalization ratio did not significantly differ between the groups (5.8% vs. 5.8%; p=0.100).

Contact with a SARS-CoV-2 positive case occurred in 138 (53.5%) cases, of which 119 (86%) were exposed to household contact. Contact history did not significantly differ between the groups (58.1% vs. 44.1%; p=0.140).

Among the 213 (82.5%) symptomatic cases, fever was significantly more common in Group 1 (68.1%) than in Group 2 (55.1%; p=0.020). However, the frequencies of other symptoms did not significantly differ between the groups (Table 1).

The laboratory findings of each group are compared in Table 2.

We used a multivariate logistic regression model to predict prolonged SARS-CoV-2 PCR positivity. This model comprised demographic features, fever, D-dimer value >0.55 mg/L, lymphopenia, and CRP level at admission. Lymphopenia was identified as an independent predictor

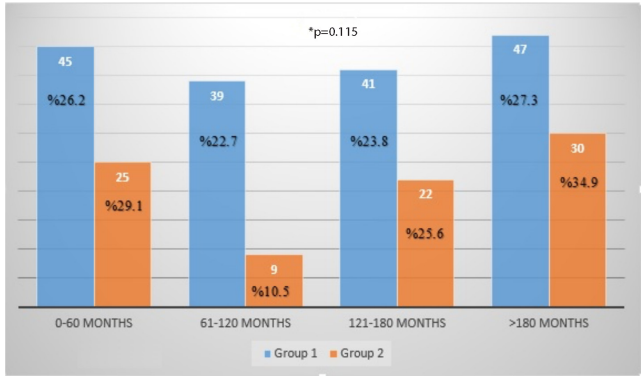

Figure 2. Comparisons of the age distribution of Groups (*Chi-square test)

of prolonged SARS-CoV-2 PCR positivity (odds ratio=2.96; 95% confidence interval: 1.08-8.13; p=0.035).

Discussion

As the primary outcome of this study, the SARS-CoV-2 PCR positivity duration was more than 14 days in 86 (16.6%) of 518 cases. Our secondary outcomes were the associations of high CRP, D-dimer >0.55 mg/L, fever, and lymphopenia with factors affecting prolonged SARS-CoV-2 PCR positivity. In addition, we identified lymphopenia as an independent risk factor.

The sex and age distributions did not significantly differ between the groups. Although no statistically significant age-related differences were identified in this study, several studies have shown that symptoms and PCR positivity depend on age (15). In addition, it has been reported that there are, on average, 10- to 100-fold greater viral loads in children aged <5 years, and COVID-19 symptoms appear in 7.4-fold more children aged <1 year (15-17). In these studies, the risk of severe symptoms was elevated in children <5 years old compared to other age groups (15-17). Hua et al. (18) found that the incubation period was longer in children than in adults. Symptoms may begin, on average, 3-7 days after a positive PCR test in some patients. Therefore, the duration of SARS-CoV-2 presence in the upper respiratory mucosa may be longer than that detected (19,20). Because studies on children and their data are limited, studies on large pediatric populations are needed.

The median duration of SARS-CoV-2 presence was

Table 1. Comparison of SARS-CoV-2 PCR positivity and symptoms

		Group 1 (n, %)	Group 2 (n, %)	p**
Service admission	Yes	10 (5.8)	5 (5.8)	0.1
	No	162 (94.2)	81 (94.2)	
†Clinical severity	Asymptomatic	25 (14.5)	20 (23.2)	0.210
	Mild	134 (77.9)	60 (69.7)	
	Modarate-severe	13 (6.7)	6 (6.9)	
Symptom	Present	147 (85.4)	66 (76.7)	0.113
	None	25 (14.6)	20 (23.3)	
*Fever and cough	Present	45 (30.6)	28 (42.4)	0.093
	None	102 (69.4)	38 (57.6)	
*Fever and cough and shortness of breath	Present	50 (34)	26 (39.4)	0.448
	None	97 (66)	40 (60.6)	
*Fever	Present	75 (51.1)	45 (68.1)	0.020
	None	72 (48.9)	19 (31.9)	
*Cough	Present	85 (57.8)	40 (60.6)	0.703
	None	62 (42.2)	26 (39.4)	
*Sore throat	Present	26 (17.7)	8 (12.1)	0.305
	None	121 (82.3)	58 (87.9)	
*Fatigue	Present	17 (11.5)	14 (21.2)	0.065
	None	130 (88.5)	52 (78.8)	
*Headache	Present	17 (11.5)	11 (16.7)	0.308
	None	130 (88.5)	55 (83.3)	
*Vomiting	Present	15 (10.2)	8 (12.1)	0.677
	None	132 (89.8)	58 (87.9)	
*Diarrhea	Present	13 (8.9)	5 (7.5)	0.758
	None	134 (91.1)	61 (92.5)	
*Myalgia	Present	11 (7.5)	5 (7.5)	0.981
	None	136 (92.5)	61 (92.5)	
*Stomach ache	Present	11 (7.5)	6 (9.1)	0.689
	None	136 (92.5)	60 (90.9)	
*Other GIS symptoms	Present	5 (3.4)	4 (6)	0.372
	None	142 (96.6)	62 (94)	

*Asymptomatic cases were excluded when comparing the presence of symptoms. **Chi-square test. †Clinical severity was determined according to the World Health Organization guidelines (14)

Table 2. Comparison of SARS-CoV-2 PCR positivity and laboratory values

	Group 1		Group 2		p-value
	§Number of patients (n)	Results	§Number of patients (n)	Results	
Leukocyte (/uL)	115	8679±3964	59	8989±3603	0.615††
Neutrophil (/uL)	115	3830 (2510-6110)	59	5176 (3180-6600)	0.239‡‡
Lymphocyte (/uL)	115	2400 (1740-3460)	59	2560 (1440-4000)	0.646‡‡
Lymphopenia (<1500/uL)	115	n=15 (13%)	59	n=15 (25.4%)	**0.043****
†LNR	115	0.63 (0.40-1.0)	59	0.55 (0.28-1.0)	0.247‡‡
†NLR	11	1.57 (0.96-2.45)	59	1.80 (0.98-3.51)	0.247‡‡
Platelets (/uL)	115	269904±75030	59	262830±80102	0.566††
Erythrocyte sedimentation rate (mm/hr)	41	9 (5-21)	22	6.5 (3.7-22.2)	0.398‡‡
Fibrinogen (mg/L)	95	332±87	36	308±87	0.102††
Fibrinogen (>300 mg/L) n, (%)	95	56 (58.9)	36	15 (41.7)	0.085**
D-dimer (mg/L)	93	0.38 (0.28-0.55)	34	0.41 (0.3-0.87)	0.884‡‡
D-dimer (>0.55 mg/L) n, (%)	93	24 (25.8)	34	14 (41.1)	**0.022****
C-reactive protein (mg/L)	119	2.1 (0.8-8.8)	61	6.2 (1.4-17.6)	**0.026‡‡**
Procalcitonin (ug/L)	86	0.03 (0.01-0.08)	40	0.04 (0.02-0.08)	0.466‡‡
Albumin (g/L)	103	44.7±2.9	49	44.9±3.6	0.641††
FAR*	88	0.074±0.021	35	0.068±0.021	**0.057††**
Ferritin (ug/L)	40	26.4 (14.6-53.9)	23	21.7 (10.9-46.6)	0.493‡‡
‡CK-MB (U/L)	95	1.1 (0.7-2.0)	42	1.4 (0.9-2.4)	0.110‡‡
Troponin (ng/mL)	99	1.90 (1.4-2.3)	42	1.90 (1.47-3.67)	0.221‡‡

*Fibrinogen albumin ratio [Fibrinogen (mg/dL)/Albumin (mg/dL)]
†Lymphocyte/neutrophil ratio and neutrophil/lymphocyte ratio
‡Creatinine kinase myocardial band
§Patients who analyzed were written separately for SARS-CoV-2 PCR positivity for ≤14 days and >14 days.
††Student's t-test, ‡‡Mann-Whitney U test, **Chi-square test
SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, PCR: Polymerase chain reaction, LNR: Lymphocyte-to-neutrophil ratio, NLR: Neutrophil-to-lymphocyte ratio, FAR: Fibrinogen albumin ratio, CK-MB: Creatine kinase-myocardial base

11.1 days (2-35 days) in all 518 patients included in this study. In addition, no virus was detected in 83.4% of the patients after day 14. The median duration of SARS-CoV-2 presence in our study is consistent with the meta-analysis conducted by Li et al. (21), who found that the mean time required for SARS-CoV-2 RNA to become undetectable in nasopharyngeal/throat swabs was 11.43 days. Another study found the median duration of viral shedding and PCR positivity in children to be seven days (5-10), with 96.3% of patients becoming negative within 14 days (22). Different studies have reported that the average duration of viral spread may be longer than 14 days, similar to our study (23,24). The longer SARS-CoV-2 presence in this study compared with others may reflect our comprehensive duration evaluation with close follow-up by performing tests at frequent intervals.

This study found no significant differences in the duration of SARS-CoV-2 presence, disease severity, or hospitalization need. We could not find published studies that determined the significance of the relationships between clinical severity and the duration of SARS-CoV-2 presence. In this study, we found that hospitalization rates for critically ill patients were low, and the rate of patients with mild symptoms was high because PCR testing was performed on all cases with complaints or contact histories. The reasons for the relatively mild disease course in children remain incompletely understood. A weaker inflammatory response and differences in the expression and regulation of angiotensin-converting enzyme 2 receptors in the airway epithelium have been suggested as causes (25,26).

In this study, the most common symptoms were fever (56.3%) and cough (58.6%); fever with cough was 34.2%, while concomitant fever, cough, and shortness of breath were 35.6%. Previous studies have reported fever (51-68%) and cough (41-61%) as the most common symptoms in children diagnosed with COVID-19 (27-29). In this study, we found that SARS-CoV-2 presence was longer in patients with fever and lymphopenia. A retrospective study in Wuhan, China, found that the median viral shedding period during COVID-19 hospitalization was longer in children with symptoms (especially fever, pneumonia, and lymphopenia), consistent with this study (30). Moreover, Lu et al. (30) found that symptomatic children had a longer

viral shedding period (17 days) than asymptomatic children (11 days). However, Korean and Kuwaiti studies found no correlation between viral shedding and symptoms (31,32). The relationship between symptoms and prolonged SARS-CoV-2 presence was not explored in this study. It should be considered that the presence of SARS-CoV-2 may last more than 14 days, especially in patients with fever signs.

In this study, high CRP levels and lymphopenia were significantly associated with prolonged SARS-CoV-2 presence. Although elevated D-dimer levels did not significantly differ between the groups, D-dimer levels >0.55 mg/L were significantly associated with prolonged SARS-CoV-2 presence. Similarly, we found that lymphopenia increased the prolonged SARS-CoV-2 presence by 2.96-fold. However, there was no relationship between age and SARS-CoV-2 presence, whereas elevated CRP levels and lymphopenia were associated with prolonged SARS-CoV-2 presence. Lu et al. (30) in Wuhan, China, found that high CRP and low lymphocyte levels correlated with the duration of SARS-CoV-2 presence in patients aged <5 years, especially those <1 year. In this study, D-dimer and fibrinogen levels were not significantly associated with prolonged SARS-CoV-2 presence (30). However, lymphopenia should be considered as an independent risk factor. We hypothesize that lymphopenia weakens the body's ability to fight the virus, thus prolonging viral persistence. In addition, there is an urgent need for more detailed studies on the relationship between D-dimer levels and prolonged SARS-CoV-2 presence.

FAR is a proportional parameter recently defined as an inflammation indicator. Studies have shown that it predicts mortality in COVID-19 patients and can be used as a marker for serious disease (33,34). In this study, FAR was marginally significant. However, we could not find any studies exploring the association between the duration of SARS-CoV-2 presence and FAR in children. Although there is no statistically significant association, we believe that FAR should be considered in these patients and requires further study.

Study Limitations

Our study was limited by its retrospective design. In addition, because this study included all children regardless of their symptoms, hospital admissions were generally late due to the difficulties children experience in expressing their complaints compared with adults. Finally, the findings of this study were impacted by the unknown number of positive days before admission. Despite these limitations, our number of cases was high compared with a pediatric study. Our study group was homogeneously distributed. We were able to show what we wanted to show about the severity of the disease and the prolongation of PCR positivity.

Conclusion

The risk of SARS-CoV-2 transmission from children should not be ignored. Understanding the duration of the SARS-CoV-2 presence is important for determining suitable isolation periods for the pediatric population. In this study, the duration of SARS-CoV-2 presence was associated with the disease's clinical findings and laboratory results. Our findings recommended more careful follow-up in pediatric patients due to prolonged SARS-CoV-2 presence for more than 14 days, especially those with fever, elevated CRP and D-dimer levels, and lymphopenia.

Ethics

Ethics Committee Approval: This study was approved by the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Clinical Research Ethics Committee (approval number: 23-2021, dated: May 5, 2021).

Informed Consent: Informed consent was obtained from the parents of all the children enrolled in this study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.O., G.A., Design: B.O., G.A., Data Collection or Processing: F.C.Y., Z.U.O., Analysis or Interpretation: B.O., F.C.Y., Z.U.O., G.A., Literature Search: B.O., F.C.Y., Z.U.O., G.A.,Writing: B.O., G.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536-44.
2. World Health Organization (2020) Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. http://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020 (Accessed on November 21, 2021).
3. Meyerowitz EA, Richterman A, Gandhi RT, Sax PE. Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors. Ann Intern Med 2021;174:69-79.
4. Geng Y, Wang Y. Stability and transmissibility of SARS-CoV-2 in the environment. J Med Virol 2023;95:e28103.
5. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. N Engl J Med 2020;382:1177-9.
6. de Hoog MLA, Sluiter-Post JGC, Westerhof I, et al. Longitudinal Household Assessment of Respiratory Illness in Children and

Parents During the COVID-19 Pandemic. JAMA Netw Open 2022;5:e2237522.

7. Dawood FS, Porucznik CA, Veguilla V, et al. Incidence Rates, Household Infection Risk, and Clinical Characteristics of SARS-CoV-2 Infection Among Children and Adults in Utah and New York City, New York. JAMA Pediatr 2022;176:59-67.
8. Riley S, Ainslie KEC, Eales O, et al. Resurgence of SARS-CoV-2: Detection by community viral surveillance. Science 2021;372:990-5.
9. Poletti P, Tirani M, Cereda D, et al. Association of Age With Likelihood of Developing Symptoms and Critical Disease Among Close Contacts Exposed to Patients With Confirmed SARS-CoV-2 Infection in Italy. JAMA Netw Open 2021;4:e211085.
10. Han MS, Choi EH, Chang SH, et al. Clinical Characteristics and Viral RNA Detection in Children With Coronavirus Disease 2019 in the Republic of Korea. JAMA Pediatr 2021;175:73-8.
11. Cai Y, Huang Z, Wu B, et al. Increased nutrition risk is associated with a prolonged negative conversion of viral RNA in children and adolescents with COVID-19. Nutr Clin Pract 2023;38:1073-81.
12. Fontana LM, Villamagna AH, Sikka MK, McGregor JC. Understanding viral shedding of severe acute respiratory coronavirus virus 2 (SARS-CoV-2): Review of current literature. Infect Control Hosp Epidemiol 2021;42:659-68.
13. T.C. Sağlık Bakanlığı Bilimsel Danışma Kurulu, COVID-19 Rehberi, Çocuk Hasta Yönetimi ve Tedavi, 2022, Ankara. Erişim Tarihi: 20.03.2023, https://covid19.saglik.gov.tr/Eklenti/42283/0/covid19rehbericocukhastayonetimivetedavi06012022v1pdf.pdf
14. Clinical management of severe acute respiratory infection when COVID-19 is suspected: Interim guidance V1.2: World Health Organization; 2020 [April 2, 2020]. (Access Date: 03.03.2023) Available from: https://www.who.int/publications/i/item/clinical-management-ofcovid-19.
15. Heald-Sargent T, Muller WJ, Zheng X, Rippe J, Patel AB, Kociolek LK. Age-Related Differences in Nasopharyngeal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Levels in Patients With Mild to Moderate Coronavirus Disease 2019 (COVID-19). JAMA Pediatr 2020;174:902-3.
16. Bayhan Gİ, Özkubat Korkmaz I, Şahiner ES, et al. Are SARS-CoV-2 viral loads in children lower than in adults? J Infect 2023;86:13-4.
17. Lota-Salvado R, Padua JR, Agrupis KA, et al. Epidemiological and clinical characteristics of children with confirmed COVID-19 infection in a tertiary referral hospital in Manila, Philippines. Trop Med Health 2023;51:9.
18. Hua CZ, Miao ZP, Zheng JS, et al. Epidemiological features and viral shedding in children with SARS-CoV-2 infection. J Med Virol 2020;92:2804-12.
19. Irfan O, Muttalib F, Tang K, Jiang L, Lassi ZS, Bhutta Z. Clinical characteristics, treatment and outcomes of paediatric COVID-19: a systematic review and meta-analysis. Arch Dis Child 2021;16:440-8.
20. Gupta V, Singh A, Ganju S, et al. Severity and mortality associated with COVID-19 among children hospitalised in tertiary care centres in India: a cohort study. Lancet Reg Health Southeast Asia 2023;13:100203.
21. Li B, Zhang S, Zhang R, Chen X, Wang Y, Zhu C. Epidemiological and Clinical Characteristics of COVID-19 in Children: A Systematic Review and Meta-Analysis. Front Pediatr 2020;8:591132.
22. Gupta ML, Gothwal S, Gupta RK, et al. Duration of Viral Clearance in Children With SARS-CoV-2 Infection in Rajasthan, India. Indian Pediatr 2021;58:123-5.
23. Luo W, Wang W, Wu D, Jian L, Lin Y, Yao X. Peripheral Lymphocyte Count and Viral Clearance in COVID-19. J Coll Physicians Surg Pak 2022;32:1637-9.
24. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe 2021;2:13-22.
25. Zimmermann P, Curtis N. Why Does the Severity of COVID-19 Differ With Age?: Understanding the Mechanisms Underlying the Age Gradient in Outcome Following SARS-CoV-2 Infection. Pediatr Infect Dis J 2022;41:36-45.
26. Koch CM, Prigge AD, Anekalla KR, et al. Age-related Differences in the Nasal Mucosal Immune Response to SARS-CoV-2. Am J Respir Cell Mol Biol 2022;66:206-22.
27. Guner Ozenen G, Sahbudak Bal Z, Bilen NM, et al. Clinical and Laboratory Findings of SARS-CoV-2 Infection in Children Younger than 6 Months Old: Neutropenia is More Common Not Lymphopenia. J Trop Pediat 2022;68:fmac041.
28. Najafinejad M, Cheraghali F, Aghcheli B, et al. COVID-19 in Pediatrics: Demographic, Clinical, Laboratory, and Radiological Characteristics of Infected Patients With SARS-CoV-2. Front Pediatr 2022;9:808187.
29. Harashchenko T, Umanets T, Podolskiy V, et al. Epidemiological, Clinical, and Laboratory Features of Children with SARS-CoV-2 in Ukraine. J Mother Child 2023;27:33-41.
30. Lu Y, Li Y, Deng W, et al. Symptomatic Infection is Associated with Prolonged Duration of Viral Shedding in Mild Coronavirus Disease 2019: A Retrospective Study of 110 Children in Wuhan. Pediatr Infect Dis J 2020;39:95-9.
31. Alsharrah D, Alhaddad F, Alyaseen M, et al. Clinical characteristics of pediatric SARS-CoV-2 infection and coronavirus disease 2019 (COVID-19) in Kuwait. J Med Virol 2021;93:3246-50.
32. Han MS, Choi EH, Chang SH, et al. Clinical Characteristics and Viral RNA Detection in Children With Coronavirus Disease 2019 in the Republic of Korea. JAMA Pediatr 2020;175:73-80.
33. Çekiç D, Emir Arman M, Cihad Genç A, et al. Predictive role of FAR ratio in COVID-19 patients. Int J Clin Pract 2021;75:14931.
34. Kuluöztürk M, Deveci F, Turgut T, Öner Ö. The Glasgow Prognostic Score and fibrinogen to albumin ratio as prognostic factors in hospitalized patients with COVID-19. Expert Rev Respir Med 2021;15:1061-8.